IN THE CLAIMS:

Please cancel claims 24 to 28 without prejudice.

REMARKS

Claims 1-33 were pending in this application. Claims 24 to 28 have been canceled without prejudice to Applicants' right to pursue the subject matter of any canceled claims in subsequent applications.

Information Disclosure Statement

In response to Examiner's request, Applicants are resubmitting all references contained in the Information Disclosure Statement filed November 10, 2000.

The Rejections Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

Claims 1 to 23, which are drawn toward methods of treating and preventing cancer in a human, stand rejected under 35 U.S.C. §112, first paragraph for containing subject matter not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. While acknowledging that the specification is enabled for a method of treating cancer, Examiner alleges that the specification does not enable a method of preventing cancer. Applicants assert that the specification enables the full scope of the claimed invention, and as such, the rejection should be withdrawn.

The invention described in the specification involves a method of treating or preventing cancer in a human using a bcl-2 antisense oligonucleotide in a cycle of therapy at a dose of 0.01 to 50 mg/kg/day for a period consisting of 2 to 13 days.

The standard for determining whether the specification meets the enablement requirement is whether any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Nevertheless, a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

Applicants point out, however, that according to the MPEP, "[w]hen considering the factors relating to a determination of non-enablement, if all other factors point toward enablement, then the absence of working examples will not by itself render the invention non-enabled."§ 2164.02. (Other factors which should be considered in making a determination of enablement include: the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. MPEP § 2164.01(a).)

Moreover,

> evidence of pharmacologic or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. *Cross v. Iizuka,* 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980). An applicant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals,) or any combination thereof. The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980).

MPEP § 2107.03. Emphasis added.

As provided by the instant specification, over-expression of bcl-2 is known in the art to not only contribute to the maintenance of the cancerous state, but to the transformation of

cells to a cancerous state (*e.g.*, over-expression of bcl-2 is implicated in causing certain leukemias, lymphoid tumors, lymphomas, neuroblastomas, and nasopharyngeal, prostate, breast and colon carcinomas.) *See* instant specification at page 1, line 29 to page 2, line 22. That is, over-expression of bcl-2 causes normal cells to be transformed to a cancerous state, ultimately leading to cancer in humans. Thus, by suppressing expression of the bcl-2 gene, the methods and compositions of the instant invention can be used to prevent the occurrence or reoccurrence of cancer in a human. Applicants submit that a reasonable correlation has been established between the activity of bcl-2 antisense oligonucleotides (suppression of bcl-2 expression) and the asserted use (prevention of cancer in a human).

Furthermore, by providing the specific compositions, dosages and routes of administration, the specification makes clear to one skilled in the art how to use antisense oligonucleotides against bcl-2 to prevent cancer in a human. Instant specification at page 12, line 20 to page 16, line 34. For example, as noted in the instant specification, examples of bcl-2 antisense oligomers that may be used in accordance with the present invention are described in detail in U.S. Patent Application Serial No. 08/217,082, now U.S. Patent No. 5,734,033; U.S. Patent Application Serial No. 08/465,485, now U.S. Patent No. 5,831,066; and U.S. Patent Application Serial No. 09/080,285, now U.S. Patent No. 6,040,181. Instant specification at page 11, lines 14-19. The specification also provides specific dosages for a given route of administration (*i.e.*, intravenously, subcutaneously or locally) for the treatment or prevention of cancer. Instant specification at page 13, line 24 to page 14, line 6. Therefore, one skilled in the art seeking to prevent cancer in a human using the methods and compositions of the instant invention need not experiment unduly, as Applicants have described in great detail how to administer bcl-2 antisense oligonucleotides for prevention of cancer in a human. Accordingly, Applicants request that Examiner's rejection of claims 1 to 23 for lack of enablement be withdrawn.

The Rejections Under 35 U.S.C. § 102(a) and (b) Should Be Withdrawn

Examiner rejects claims 1 to 5, 13 to 18, 24 to 28 and 31 to 33 under 35 U.S.C. § 102 as being anticipated by Webb *et al.*, 1997, Lancet 349:1137-1141 ("Webb"), Waters *et al.*, 2000, J. Clin. Onc 18:1812-1823 ("Waters"), or Morris *et al.*, 1999, Proc. Am. Soc. Clin. Onc. 18:323a ("Morris").

Further, Examiner rejects claims 1 to 6, 9 to 12, 13 to 19, 24, 26 to 29 and 31 to 33 under 35 U.S.C. § 102 as being anticipated by Jansen *et al.*, 1999, Proc. Am. Soc. Clin. Onc. 19:531a ("Jansen I") or Jansen *et al.*, 2000, Lancet 356:1728-33 ("Jansen II").

The claimed invention relates to methods of treating or preventing cancer in a human by administering a bcl-2 antisense oligonucleotide in one or more cycles of therapy at a dose of 0.01 to 50 mg/kg/day or 10 to 50 mg/kg/day for a period consisting of 2 to 13 days (claims 1 to 18), methods of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide in combination with one or more chemoagent wherein said chemoagent is administered at a reduced dose (claims 19 to 23), and pharmaceutical compositions of a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day or 10 to 50 mg/kg/day in combination with a reduced dose of a cancer therapeutic agent (claims 29 to 33).

"To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently." *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). None of the references cited by Examiner, however, contain each and every element of the claimed invention as required for anticipation.

Webb discloses a treatment protocol wherein a bcl-2 antisense oligonucleotide is administered at dosages of 4.6 to 73.6 mg/m^2 for 14 days. Webb does not describe treating or preventing cancer in a human for a period less than 14 days. Thus, Webb does not anticipate claim 1 and dependent claims 2 to 5 and 13 to 18. Nor does Webb describe administering a

bcl-2 antisense oligonucleotide in combination with a cancer therapeutic agent as required by claims 31 to 33. Thus, Webb does not anticipate these claims.

Waters discloses a protocol wherein a bcl-2 antisense oligonucleotide was administered to patients at doses of 4.6 to 195.8 mg/m^2/day for 14 days. Waters does not disclose or suggest a regimen for treating or preventing cancer lasting less than 14 days. Thus, Waters does not anticipate claim 1 and dependent claims 2 to 5 and 13 to 18. Nor does Waters describe administering a bcl-2 antisense oligonucleotide in combination with a cancer therapeutic agent as required by claims 31 to 33. Thus, Waters does not anticipate these claims.

Morris discloses continuous intravenous infusion of bcl-2 antisense oligonulceotides at doses ranging from 0.6 to 2.3 mg/kg/day for 14 days in patients with advanced solid tumors. Morris does not disclose or suggest a method of treating or preventing cancer using a treatment cycle of less than 14 days. Thus, Morris does not anticipate claim 1 and dependent claims 2 to 5 and 13 to 18. Nor does Morris describe administering a bcl-2 antisense oligonucleotide in combination with a cancer therapeutic agent as required by claims 31 to 33. Thus, Morris does not anticipate these claims.

Jansen I discloses a study of a combination therapy of a bcl-2 antisense oligonucleotide and dacarbazine in patients with advanced malignant melanoma over a 14 day period. Jansen I does not disclose a regimen for treating or preventing cancer lasting less than 14 days, and does not anticipate claim 1 and dependent claims 9 to 12 and 13 to 18. Further, the dose of dacarbazine used in Jansen I was *per* the "standard dacarbazine regimen (200mg/m^2 X 5 days)." Emphasis added. Thus, Jansen I does not describe a reduced dose of a cancer therapeutic agent (defined in the instant specification at page 7, lines 11-19) as required by claims 19, 29 and 31 to 33. As such, Jansen I does not anticipate these claims.

Applicants point out that Jansen II was published on November 18, 2000, which postdates the instant application's filing date of November 10, 2000. Jansen II is therefore not prior art *vis-à-vis* the instant application. Examiner's rejection in light of Jansen II should therefore be withdrawn.

The Rejections Under 35 U.S.C. § 103 (a) Should be Withdrawn

Examiner rejects claims 1-33 as obvious under 35 U.S.C. § 103 (a) in light of Raynaud *et al.*, 1997, J. Pharm. Exp. Ther. 281:420-427 ("Raynaud"), in further view of Lopes de Menezes *et al.*, 2000, Clin. Cancer Res. 6:2891-2902 ("Lopes de Menezes"), Miayake *et al.*, 2000, J. Nat. Cancer. Inst. 92:34-41 ("Miayake"), Cotter *et al.*, 1999, Biochimica Biophysica Acta, 1489:97-106 ("Cotter"), Webb et al., 1997, The Lancet 349: 1137-1141 ("Webb") and U.S. Patent 6,214,986 to Bennett ("Bennett").

A finding of obviousness under 35 U.S.C. § 103 requires a determination that the scope and content of the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1 (1966). The relevant inquiry is whether the prior art both suggests the invention, and provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As discussed more fully below, none of the references cited by Examiner make obvious the claimed invention. First, there is no suggestion or motivation in any of the references to modify the reference or to combine references. Second, far from giving one skilled in the art a reasonable expectation of success, the references taken as a whole actually

teach away from the methods and compositions of the instant invention. Finally, none of the references either alone or in combination, teach or suggest a method of treating or preventing cancer in a human using a short treatment cycle lasting between 2 and 13 days and administering high doses of bcl-2 antisense or to combine the dose of bcl-2 antisense oligonucleotide with a reduced dose of a cancer therapeutic agent.

Raynaud describes a study in which mice were injected with a continuous subcutaneous infusion of a bcl-2 antisense oligonucleotide at a dose of approximately 5 mg/kg for 7 days in order to determine the pharmacokinetics of the bcl-2 antisense oligonucleotide. Raynaud taken alone or in combination with any or all of the cited references does not render obvious the claimed methods of treating or preventing cancer in a human. Indeed, Raynaud actually discourages combining it's teachings with the other studies. Raynaud cautions that the results of such phamacokinetic studies cannot be broadly applied across different experimental conditions and that further study is required. Specifically, Raynaud notes that "[l]arge pharmacokinetic variations have been recorded in various studies reflecting size, structure, dose of oligonucleotide used and species studied (mouse, rat or monkey)," (Raynaud at page 424, col. II, last paragraph).

Lopes de Menezes describes a mouse model to assay the activity of a bcl-2 antisense oligonucleotide combined with doxarubicin. In the study, the mice were treated with a bcl-2 antisense oligonucleotide over a 19 day span. The study concludes that "we demonstrated that daily i.p. [bcl-2 antisense oligonucleotide] treatment administered over 3 weeks was capable of achieving significant protein down-regulation in human breast xenograft solid tumors, and this was associated with antitumor activity." Lopes de Menezes at page 2900, col. II, first full paragraph. Emphasis added.

Lopes de Menezes does not disclose or suggest treatment or prevention of human cancer using a treatment cycle of less than 14 days, as does the instant invention, since it

demonstrates effective treatment in mice using a bcl-2 antisense oligonucleotide administered over 3 weeks. Additionally, the dosages of doxarubicin administered in Lopes de Menezes were set at the maximum tolerated dose. Thus, Lopes de Menezes does not teach or suggest to one skilled in the art combining a bcl-2 antisense oligonucleotide with a reduced dose of a cancer chemotherapeutic agent.

Miayake discloses *in vivo* administration of bcl-2 antisense oligonucleotides and paclitaxel in tumor bearing mice. Mice were injected once daily with bcl-2 antisense oligonucleotide at a dose of 12.5 mg/kg over a 14 day period and once daily with 0.5 mg of paclitaxel. Results demonstrated that combined therapy in mice resulted in enhanced tumor mass reduction and recurrence-free survival when compared to treatment with the antisense oligonucleotide or paclitaxel alone. *See* Miayake at Fig. 4, page 38.

Miayake does not disclose or suggest to one skilled in the art that cancer can be treated or prevented in a human using a treatment cycle shorter than 14 days. Furthermore, Miayake does not teach or suggest to one skilled in the art combining a bcl-2 antisense oligonucleotide with a reduced dose of a cancer therapeutic agent to treat a human.

Webb and Cotter both disclose phase I trials of bcl-2 antisense oligonucleotides administered to humans with cancer in treatment cycles lasting 14 days. Both references disclose that the antisense oligonucleotide was well tolerated and exhibited low toxicity. Neither Webb nor Cotter, however, teach or suggest to one skilled in the art a treatment cycle lasting 2 to 13 days for treating or preventing cancer in a human. Furthermore, Cotter teaches away from the high dosage of bcl-2 antisense oligonucleotide, short duration methods and compositions of the instant invention. Specifically, Cotter notes that "[a]n important aim of this phase I study was to establish toxicity of Bcl-2 antisense oligonucleotides. A maximum tolerated dose has been established at 4 mg/kg/day." Cotter at page 104, col. I, first full paragraph.

Moreover, Cotter's trial was self-admittedly designed after a murine model in which it took 3 weeks of treatment for complete eradication of the cancer. *See* Cotter at page 99, col. II, first full paragraph and page 100, col. II, second full paragraph. In fact, Cotter stresses that a longer treatment cycle using a lower dose of bcl-2 antisense oligonucleotide is the preferred method of treatment. ("These results suggest that duration of treatment may be as important as the dosage and certainly considerably less antisense is required to give complete disease eradication, with a 3 week infusion compared to 2."). *See* Cotter at page 99, first full paragraph. Thus, Cotter would not provide one skilled in the art a reasonable expectation of success in treating or preventing cancer using a treatment cycle shorter than 2 weeks and actually teaches away from the shortened treatment regimen of the claimed invention.

Bennett describes compositions of bcl-x antisense oligonucleotides and methods of inhibiting expression of bcl-x in cells or tissue *in vitro*. Bennett does not teach or suggest methods of treatment or prevention of human cancer *in vivo* using bcl-2 antisense oligonucleotides and does not cure any of the deficiencies of the art relied on by the Examiner to render the claimed invention obvious.

The art cited by the Examiner taken either alone or in combination does not render the methods of treating or preventing cancer in a human by administering high doses of bcl-2 antisense over a shortened period of time, as claimed obvious. Raynaud, Lopez de Menezes and Miayake are all mouse studies in which the antisense oligonucleotide was administered for a period of time ranging from one week (Raynaud) to 14 to 19 days (Lopez de Menezes, Miayake). Raynaud expressly states that its teachings cannot be applied to other animal models, let alone humans. Lopez de Menezes and Miayake describe treatment regimens in mice that are longer those claimed and include administering maximum doses of chemotherapeutics. As demonstrated by Cotter, while many of the animal models show a reduction in tumor growth at two weeks, complete eradication is observed at three weeks.

(Cotter at page 99). Thus, one skilled in the art designing regimens for treating humans would opt for longer treatment regimens, not the shortened treatment regimens of the claimed invention. Cotter further teaches away from the invention in that lower doses of bcl-2 antisense are administered due to potential toxicity issues, not the high levels of bcl-2 antisense as the claimed methods require. Webb describes a study where patients are treated for 14 days, and does not provide the suggestion or motivation to shorten the treatment regimen which is lacking in the art cited by the Examiner. Finally, Bennett does not teach or describe methods of treating cancer using bcl-2 antisense oligonucleotides, and as a result does not cure any of the deficiencies of the art relied on by the Examiner, taken alone or in combination, to render the claimed invention obvious.

Further, Applicants point out that the claimed invention "yields unexpectedly improved properties" and thus would not have been obvious to one skilled in the art. MPEP § 2144.08 (B); *see also* MPEP § 2144.09. Example 1 of the instant specification, a clinical study using the methods of the instant invention, demonstrates that "when a bcl-2 antisense oligomer is administered in high doses for short periods of time, the treatment exhibits low toxicity as scored by common toxicity criteria, reduces BCL-2 within the tumor, facilitates apoptosis, and leads to objective tumor responses and prolonged patient survival." Instant specification at page 30, lines 17-21. Emphasis added. Thus, Applicants submit that the high dosage, short treatment cycle methods of the instant invention demonstrate "unexpectedly improved properties" over the teachings of the prior art and therefore, would not have been obvious to one skilled in the art.

Accordingly, Applicants respectfully submit that Examiner's rejection of claims 1 to 33 as obvious in view of the cited art should be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants believe that each ground for rejection or objection has been overcome or obviated, and that all of the pending claims are in condition for allowance. Applicants respectfully request consideration of the pending claims and withdrawal of the rejections. An early allowance is earnestly sought.

Respectfully submitted,

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Enclosure